



Retrospective Evaluation of the Preoperative Features of Breast Cancer and Sentinel Lymph Node Metastasis

Meme Kanserinde Sentinel Lenf Nodu Metastazının Preoperatif Özelliklerinin Retrospektif Değerlendirilmesi

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Abstract

Objective: Determining the presence of metastasis in the axillary lymph nodes using preoperative data in breast cancer has been studied previously. Formulas and nomogram programs that calculate the relationship between parameters and axillary lymph node metastases are presented. It is controversial whether current calculations give the same accuracy across all ethnic groups. We aimed to validate the Memorial Sloan Kettering Cancer Center (MSKCC) nomogram results for the prediction of sentinel lymph node (SLN) metastasis in patients with breast cancer in Turkey.

Method: The clinical records, pathology results, and surgery reports of 400 patients who underwent surgery were examined. Sensitivity, specificity, positive and negative predicted values, and area under the curve (AUC) values were calculated using a nomogram developed by the MSKCC.

Results: Frozen section results of SLN examination of the patients were positive in 101 of the 400 patients. The relationship between nomogram calculation and sentinel positivity was evaluated using the receiver operating characteristic curve (ROC); AUC 0,699, $p < 0.001$. When sentinel lymph node biopsy (SLNB) status and nomogram risk ratio were compared, the sensitivity was calculated as 85% and the specificity was 40%. The negative predicted value was 68% and the positive predicted value was 63%. The ROC curve calculation reached a risk value of 77% as the optimal criterion. When this value was reached, the nomogram's sensitivity was 96% and specificity was 14.8%.

Conclusion: Although there was a significant relationship in the calculation of MSKCC nomograms in our patient group, it was found to show an excessive risk of metastasis. Both sensitivity and specificity

Öz

Amaç: Meme kanserinde aksiller lenf nodu metastazı riskini hesaplayan formüller ve nomogram programları sunulmuştur. Mevcut hesaplamaların tüm etnik gruplarda aynı doğruluğu verip vermediği tartışmalıdır. Türkiye'deki meme kanserli hastalarda sentinel lenf nodu metastazı (SLNB) öngörüsünde Memorial Sloan Kettering Kanseri Merkezi (MSKCC) nomogram sonuçlarını doğrulamak istedik.

Yöntem: Cerrahi kliniğimizde ameliyat edilen 400 hastanın klinik kayıtları, patoloji sonuçları ve ameliyat raporları incelendi. Duyarlılık, özgüllük, pozitif ve negatif öngörü değerleri ve eğri altındaki alan (AUC) değerleri MSKCC tarafından geliştirilen nomogram kullanılarak hesaplandı.

Bulgular: Hastaların SLN incelemesinin frozen kesit sonuçları 400 hastanın 101'inde pozitif. Nomogram hesaplaması ile sentinel pozitifliği arasındaki ilişki, alıcı işletim karakteristik eğrisi (ROC) kullanılarak değerlendirildi; AUC 0,699, $p < 0,001$. Sentinel lenf nodu biyopsisi (SLNB) durumu ile nomogram risk oranı karşılaştırıldığında duyarlılığı %85, özgüllüğü %40 olarak hesaplandı. Negatif yüklemli değer %68, pozitif yüklemli değer ise %63 oldu. ROC eğrisi hesaplaması optimal kriter olarak %77 risk değerine ulaştı. Bu değere ulaşıldığında nomogramın duyarlılığı %96, özgüllüğü ise %14,8 idi.

Sonuç: Hasta grubumuzda MSKCC nomogramlarının hesaplanmasında anlamlı ilişki olmasına rağmen aşırı metastaz riski gösterdiği tespit edildi. Özellikle optimal risk değerleri dikkate alındığında hem duyarlılık hem de özgüllük değerleri batılı çalışmalara göre anlamlı derecede düşük bulunmuştur. Sonuçlarımızın Avrupa ve Amerika popülasyonlarını temel alan çalışmalarla karşılaştırıldığında Asya popülasyonu üzerine yapılan çalışmalara daha benzer olduğu görüldü. Farklı etnik popülasyonların



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values were found to be significantly lower than those in western studies, especially when optimal risk values were considered. Our results were found to be more similar to the studies on the Asian population when compared with the studies based on European and American populations. It was concluded that different ethnic populations may have their own characteristics and that a nomogram calculation that is specifically designed for each ethnic population may be required.

Keywords: Breast cancer, breast surgery, nomogram, sentinel lymph node

Introduction

Axillary lymph node metastasis is one of the most important prognostic factors in breast cancer patients. Primary breast cancer most often metastasizes to axillary lymph nodes (1,2). Ninety-five percent of women who die from breast cancer have axillary lymph node metastases, and the most important factor in determining prognostic factors and providing cures is the presence of metastases at the Axillary lymph nodes (3). While the risk of recurrent cancer in patients with axillary lymph node metastasis is above 75%, the same risk decreases to 30% in patients with non-metastatic axillary lymph nodes

Axillary lymph node dissection leads to high morbidity and is not necessary in every patient. For this reason, sentinel lymph node biopsy (SLNB) has been replaced with axial dissection in patients with early breast cancer because of its less invasive nature and highly accurate results (4-7).

The Memorial Sloan Kettering Cancer Center nomogram calculation is one of the most widely used international validation nomogram studies. In studies conducted on the American population, preoperative parameters of the patients were investigated and statistical formulas were created (8). In our study, the validity of this nomogram on the Turkish population was investigated.

Although the MSKCC nomogram was based on nine parameters, we also investigated possible connections by adding other parameters. In our study, age, tumor type, tumor size, palpability, tumor location, number of tumors, presence of necrosis, presence of ductal carcinoma *in situ* (DCIS) component, estrogen receptor (ER) -progesterone receptor (PR)- human epithelial growth factor 2 receptor (HER2) presence, Ki-67 index, lymphatic-neural invasion presence, grade of tumor data, and sentinel lymph node positivity were compared.

Materials and Methods

Clinical records, pathology results, and surgery reports of 400 patients with breast cancer who underwent surgery

kendine has özellikleri olabileceği ve her etnik popülasyona özel tasarlanmış bir nomogram hesaplamasının gerekli olabileceği sonucuna varılmıştır.

Anahtar kelimeler: Meme cerrahisi, meme kanseri, nomogram, sentinel lenf nodu

were examined. Female patients and those who underwent peroperative SLNB were included in the study. Patients with the following criteria were excluded from the study: Patients who received neoadjuvant chemotherapy treatment, patients with previous breast cancer history, and patients who underwent breast or axillary surgery previously. Before starting the incision, 5 cc of methylene blue (Blumet 100 mg/10 mL Vem pharmaceuticals İstanbul/Turkey) was injected in equal amounts at the 3, 6, 9, and 12 o'clock dials on the edge of the areola. The SLNB procedure was performed within the next 5 min. Following the axillary incision, the axillary lounge reached and sentinel lymph nodes, which were stained with methylene blue, were longitudinally directed and submitted to the frozen section evaluation. The pathologist (Ç.V.), stained the specimens with hematoxylin and eosin and examined for metastases. SLN metastases were classified as macrometastasis for diameter ≥ 2 mm, micrometastasis for diameter 2 mm, and isolated tumor cells for clusters that did not meet the micrometastasis criteria and were 2 mm in diameter. Patients with macrometastasis underwent ALND.

All patients underwent surgery using the same surgical procedures, either conservative surgery or total mastectomy. For non-palpable breast lesions, a guided wire was used.

This study was approved by the Ethics Committee of Kocaeli University Faculty of Medicine on 18.06.2020 with number 212 (KÜ GOKAEK 2020/212). This study was conducted in accordance with the Declaration of Helsinki.

Statistical Analysis

Calculations were made using a nomogram that is available on the MSKCC website (<http://nomograms.mskcc.org/breast/BreastSLNodeMetastasisPage.aspx>) (age, tumor size, tumor type, tumor placement-upper inner quadrant, lymphatic-neural invasion presence, multifocality, tumor type and grade, ER and PR presence). In addition, palpability, necrosis presence, DCIS component presence, HER2 receptor presence, and Ki-67 index were determined and their relationship with sentinel lymph nodule positivity was

evaluated. Non-nomogram parameters did not participate in sensitivity, speciality, positive and negative predicated values, or receiver operating characteristic (ROC)- area under the curve (AUC) calculation.

Statistical evaluation was performed using the IBM SPSS 20.0 (IBM Corp., Armonk, NY, USA) package program. The normal dispersion conformity test was evaluated using the Kolmogorov-Smirnov test. Numerical variables are given as median (25th-75th percentile) and frequency (percentages). For numerical variables that did not have normal distribution, Fisher's Exact, Yeates' kihar test, Pearson's chi-squared, and Monte Carlo's chi-squared tests were used in categorical variables with the Mann-Whitney U test. ROC analysis was used in sentinel metastasis groups to determine sensitivity, specificity, and cut-off points of nomogram values. The optimal cut-off value was determined using ROC analysis and AUC values. $p < 0.05$ was considered sufficient for statistical significance in two-way tests.

Results

Four hundred patients were included in the study after removing those who did not meet the criteria. When the demographic characteristics of the patients who participated in the study were examined, the mean age was evaluated as 55 (Table 1). Invasive ductal breast cancer was found in 77% of the patients (308 of 400). In 61% of the patients (244 of 400 patients), the tumor was 2 cm, and 1.5% (in 6 of 400 patients) of the patients had a mass >5 cm (Table 1). In 64.5% of patients (258 of 400), the tumor was palpable on preoperative examination (Table 1). In 64.3% of the patients, the tumor was on the upper outer quadrant (Table 1). In 89.3% (357 of 400) of the patients, a single mass and multiple lesions were detected in the remaining patients (43 of 400). The necrosis component was present in 17.2% of patients (69 of 400) (Table 1). The DCIS component accompanying the tumor was observed in 61% (244 of 400) of the patients. ER positive was observed in 82.8% (331 of 400) of patients and PR positive in 77.5% (310 of 400). HER2 was positive in 30% (120 of 400) of patients. In 77.5% (310 of 400) of the patients, the Ki-67 index was above 30%, and a significant association was found with sentinel lymph node positivity (Table 1). Tumor grades in patients were detected as grade 1 in 27.3%, grade 2 in 47.8%, and grade 3 in 25%. Lymphatic invasion was found in 26% (144 of 400) of patients, and a significant association was found with sentinel lymph node positivity (Table 1). Neural invasion was observed in 18.8% (75 of 400) of the patients, and a

significant association was found with sentinel lymph node positivity (Table 1).

In 101 of the 400 patients (25.25%), the sentinel lymph nodes were positive. The relationship between nomogram percentage and sentinel lymph node positivity was

Table 1. Demographic features of patients included in the study

Variable		SLNB -	SLNB +
Age	≤30	6	2
	31-40	35	13
	41-50	77	27
	51-60	82	26
	61-70	63	15
	71+	36	18
Tumor size	≤2 cm	193	52
	2-5 cm	102	7
	>5 cm	4	2
Palpabilite	Yes	189	69
	No	37	5
Tumor location	UOQ	187	70
	UIQ	28	5
	IOQ	46	11
	IIQ	27	11
	Central	11	4
Multifocality	Yes	32	11
	No	67	90
Operation	Lumpectomy	247	71
	Mastectomy	52	30
Histotype	Ductal	291	98
	Lobular	6	3
	Other	2	0
Grade	Low (1-2)	230	70
	High (3)	69	31
ER	+	242	89
	-	57	12
PR	+	223	87
	-	76	14
HER2	+	94	26
	-	205	75
Lymphovascular invasion	+	89	55
	-	210	46
Necrosis component	+	40	29
	-	259	72
DCIS component	+	175	69
	-	124	32
Ki-67 index	High	223	87
	Low	76	14
Neural invasion	+	45	30
	-	254	71

SLNB: Sentinel lymph node biopsy, ER: Estrogen receptor, PR: Progesterone receptor, HER2: Human epidermal growth factor 2, DCIS: Ductal carcinoma *in situ*

evaluated using the ROC curve. AUC 0.699 was found to be $p < 0.001$ (Table 2, Figure 1). A risk ratio of 77% or more was calculated in the nomogram as the optimal criterion (Table 2). When the SLNB status and nomogram risk ratio were compared, the sensitivity was calculated as 85% and the specificity was 40%. The negative predicated value was calculated as 68% and the positive predicated value was 63%. The ROC curve calculation reached a risk value of 77% as the optimal criterion. When this value was reached, the nomogram's sensitivity was 96% and its specificity was 14.8%.

Table 2. ROC of the study

ROC curve	
Variable	Nomogram
Classification variable	Sentinel lymph node metastasis
Number of instances	400
SLNB positive group	101 (25.25%)
SLNB negative group	299 (74.75%)
Prevalence of disease (%)	25.3
Area under the ROC curve (AUC)	0.699
Standard error	0.0285
95% confidence interval	0.652 to 0.744
95% bootstrap CI	0.646 to 0.751
Z statistic	7.001
Significance level p (area=0.5)	<0.0001
Optimal criterion	0.77
95% safe interval	>0.728668183 to >0.89

SLNB: Sentinel lymph node biopsy, ROC: Receiver operating characteristic, CI: Confidence interval, AUC: Area under the curve

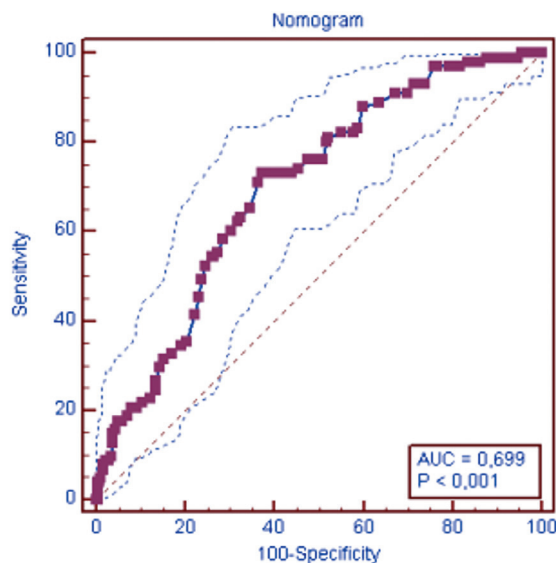


Figure 1. Area under the curve (AUC) graphics of the study

Discussion

Detecting metastasis in the axillary lymph nodes in patients with breast cancer during preoperative evaluation has been the subject of many studies. It is controversial whether current calculations give the same accuracy across all ethnic groups, and according to our knowledge, no nomogram calculation specific to the Turkish population exists. The MSKCC nomogram calculation is one of the most used international validation nomograms (8). In our study, the validity of this nomogram on the Turkish population was investigated. From the parameters that we have added within the nomogram; necrosis component, high Ki-67 index, and lymphatic and neural invasion were found to be directly related to sentinel lymph node positivity. When looking at the average age, most patients were approximately 41-50 and 51-60 years old, while the median value was calculated as 55. The current data showed that the age range most commonly seen with breast cancer was similar to national cancer data from China, Japan, and America (9,10). Because of the study, the ROC curve value was calculated as 0.699. Considering that 0.5 is a 50% chance and 1 result is a definitive diagnosis, the result of the study gives a meaningful estimate value but casts doubt on its validity in our population.

From similar studies, Vieni et al. (11) used the MSKCC nomogram in 175 patients in Palermo; When AUC value was calculated as 0.885% and the cut-off value was calculated as 50%, 81.4% specificity, 92.3% sensitivity, 80% positive predicated, and 92.9% negative predicated values were calculated. In the study of Qiu et al. (12), 1227 patients in Shunung in the People's Republic of China, the AUC calculated the value as 0.73. At their optimal criterion ratio of 70%, a predicated rate of 96% was found. Although the results were not exactly the same, they were found to have more similar characteristics to those performed in the Asian population.

Ki-67 proliferation index is often associated with poor prognosis in patients with breast cancer. In the study of Chung et al. (13), 367 patients from Seoul found a relationship between the Ki-67 proliferation index and SLN metastasis ($p=0.038$). Similar to similar studies in the literature, our study found an increased risk of axillary metastasis in patients with a high Ki-67 index (13,14). However, studies that have not found a link between the Ki-67 proliferation index and SLN metastasis are also present in the literature, including the study of the Milan group of 4351 patients (15).

Nomogram gave high sensitivity results in our patient group but showed low specificity values, as opposed to European research. Sentinel lymph node metastasis risk has been shown in similar studies of tumors with lymphovascular invasion. In a study of 4.351 patients in Milan, Viale et al. (15) evaluated lymphovascular insulation as the strongest independent parameter in sentinel lymph node metastasis. The lymphovascular invasion relationship has been reported in studies both in our country and in Canada. These studies include those of Ozmen et al. (16) in 400 patients in İstanbul and 3786 patients at MSKCC NY. In our study, SLNB positivity increased significantly in patients with lymphovascular invasion (13-18).

A limited number of studies have investigated the link between tumor necrosis and axillary lymph node metastasis. In a study following DCIS cases with microinvasion, no association was found between comedo necrosis and axillary lymph node metastasis (19). In our study, lymphatic invasion (26%) and neural invasion (18.8%), Ki-67 index elevation (77.5%) and necrosis presence (17.2%) were found to be associated with SLN positivity.

Perineural invasion has been frequently associated with lymphatic tumor emboli in high-grade tumors. In our study, we frequently monitored lymphovascular invasion in patients with perineural invasion (20).

In patients with breast cancer; age, ER, PR, HER2 conditions, and race affect prognosis. While the triple-negative phenotype was predominant in African-American breast cancer patients, most cases in Asian countries were ER- and PR-negative and HER2-positive (21). In our study, it was found that most of the cases were ER and PR positive.

The surgical dissection techniques are also shown to make significant differences between the published articles. In our center, all blue-stained SLNs were dissected; however, in some centers, reaching a certain number of SLNs is considered sufficient. As a result, the number of SLNs dissected and excised may change the nomogram accuracy because increasing the number of non-SLNs involved may correspond to fewer SLNs being removed (22).

Study Limitations

In this study, SLNB was performed using methylene blue alone. Despite the limitations of the study, it is available in the literature that methylene blue alone is a safe, cost-effective, and successful method in the progression of sentinel lymph node metastasis of breast cancer (23,24).

Conclusion

Although there was a significant relationship in the calculation of MSKCC nomograms in our patient group, it was found to show an excessive risk. Similar studies found that different results were calculated for different races. Our results were found to be more similar to studies on the Asian population compared to studies based on European and American populations. It was concluded that different ethnic populations may have their own characteristics and that a nomogram calculation that is specifically designed for each ethnic population may be required. Parameters apart from the current nomogram values might be meaningful for these populations. Prospective studies on this subject should be planned in different centers across the country, and the meaningful results that we found should be strengthened.

Ethics

Ethics Committee Approval: This study was approved by the Ethics Committee of Kocaeli University Faculty of Medicine on 18.06.2020 with number 212 (KÜ GOKAEK 2020/212). This study was conducted in accordance with the Declaration of Helsinki.

Informed Consent: Retrospective study.

Authorship Contributions

Surgical and Medical Practices: A.K., N.Z.C., N.Z.U., Concept: A.K., K.K., N.Z.U., Design: A.K., K.K., Data Collection or Processing: A.K., N.Z.C., N.Z.U., Analysis or Interpretation: A.K., N.Z.C., N.Z.U., Literature Search: A.K., K.K., N.Z.U., Writing: A.K., K.K.

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